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Original Article

Association Between Eosinophilia and Late-onset Circulatory Collapse in Preterm Infants: A case-Control Study

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Late-onset circulatory collapse (LCC) in preterm infants is presumably caused by relative adrenal insufficiency. Because eosinophilia is known to be associated with adrenal insufficiency, we attempted to clarify the relationship between eosinophilia and LCC in preterm infants. We divided the cases of the infants (born at < 28 weeks' gestation) admitted to our neonatal intensive care unit in 2008-2010 into 2 groups: those diagnosed with LCC that received glucocorticoids (LCC group), and those who did not receive glucocorticoids (control group). We compared eosinophil counts between the 2 groups and between before and after glucocorticoid treatment in the LCC group. A total of 28 infants were examined: LCC group (n = 12); control group (n = 16). The peak eosinophil counts of the LCC group were significantly higher than those of the control group (median: 1.392×10^9/L vs. 1.033×10^9/L, respectively; $p = 0.02$). Additionally, in the LCC group, the eosinophil counts declined significantly after glucocorticoid treatment (0.877×10^9/L vs. 0.271×10^9/L, $p = 0.003$). Eosinophil counts in the LCC group were significantly higher than in the control group and decreased rapidly after glucocorticoid treatment. These results indicate that eosinophilia may be a factor associated with LCC caused by adrenal insufficiency.

Key words: late-onset circulatory collapse, preterm infant, eosinophilia, steroid, adrenal insufficiency

Neonatal eosinophilia, which is defined as an eosinophil count exceeding 0.7×10^9/L, is estimated to occur in 14-76% of preterm neonates [1-4]. Eosinophilia in preterm infants is considered a transient condition after birth because in most cases, the eosinophil count returns to normal by the time of discharge from the neonatal intensive care unit (NICU). However, considerable morbidities are associated with eosinophilia in preterm infants, and the morbidities increase with prematurity. Chronic lung disease [5-7], parenteral nutrition [4], infection [8, 9], and blood transfusion [1] are correlated with eosinophilia; however, the underlying pathophysiology of eosinophilia in preterm infants has not been fully elucidated. Elevated eosinophil counts in peripheral blood may reflect adrenal insufficiency [10]. Glucocorticoids, the most effective therapy for eosinophilia, suppress cytokines that induce eosinophil production and shorten the cytokines' lifespans.

Late-onset circulatory collapse (LCC) is a disorder that occurs suddenly, manifests as hypotension and oliguria, and results in shock among preterm infants who survive the acute stage after birth [11, 12]. The most severe complication of LCC is periventricular leukomalacia. The synthesis of progesterone from pregnenolone is catalyzed by 3β-hydroxy-steroid dehydrogenase (3β-HSD), which has limited activity before

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35 weeks of post-conceptual age. Fetal cortisol synthesis takes place in the placenta [11, 13]. The lack of progesterone from the placenta after birth causes relative adrenal insufficiency that induces LCC in extremely preterm infants [14]. LCC includes systemic vasodilation, and hydrocortisone is reported to be a highly effective treatment [15].

We hypothesized that adrenal insufficiency in extremely preterm infants would induce elevated eosinophil counts. However, there are no reports on the eosinophil counts of infants with LCC. In the present study, we aimed to elucidate the relationship between eosinophilia and LCC in preterm infants.

Subjects and Methods

This was a single-center retrospective study. Data were collected from medical records of infants born before 28 weeks' gestation and hospitalized in the NICU of Tokyo Women's Medical University Hospital during the period from February 2008 to October 2010. This study was approved by the Internal Review Board of Tokyo Women's Medical University. Written informed consent was obtained from the parents of the patients. Infants with congenital anomalies, chromosomal abnormalities, or severe intraventricular hemorrhage (grade III or IV) were excluded. Intraventricular hemorrhage was diagnosed by intracranial echography and categorized as grade I-IV based on diagnostic criteria [16]. Respiratory distress syndromes were diagnosed by stable microbubble rating and chest X-ray before surfactant administration. Chorioamnionitis was diagnosed by histological examination of the placenta.

Blood cell counts were analyzed every 2 weeks (±7 days) and as needed. Automated blood cell counters (XE5000, Sysmex, Lincolnshire, IL, USA) were used to analyze white blood cell counts. Eosinophils were counted by trained lab technicians.

Infants who fulfilled the criteria for LCC (Table 1) [11] were administered a physiological dose of hydrocortisone (1-2 mg/kg/dose).

The LCC group was composed of infants diagnosed with LCC and treated with steroids. Infants who had not undergone steroid treatment were assigned to the control group. The 'pre-steroid eosinophil counts' were evaluated using blood samples collected within 1 week before steroid administration in the LCC group. The 'post-steroid eosinophil counts' were evaluated using blood samples collected within 3-24 h after steroid administration. We compared "the pre-steroid eosinophil counts and post-steroid eosinophil counts in the LCC group. In the LCC group, the eosinophil counts at LCC onset and those within 24 h after the first steroid treatment were used for the analysis, whereas those at recurrence were excluded. We also compared the highest eosinophil counts during hospitalization between the LCC and control groups.

To evaluate the characteristics of the infants, we conducted a statistical analysis using the Chi-squared and Kruskal-Wallis tests (IBM SPSS® Statistics v.24). To evaluate the eosinophil counts, which are nonparametric data, the statistical analysis was performed using the Mann-Whitney *U*-test. The statistical significance level was set at $p < 0.05$.

Results

During the study period, 56 infants were included, of which 40 were administered steroid treatment at least once during their hospitalization; among these, 18 infants were diagnosed with LCC. Twelve infants whose eosinophil counts were measured before LCC (within 1 week before steroid treatment) and after steroid treatment (3-24 h after steroid treatment) were classified as the LCC group. A total of 16 patients who did not receive steroid treatment were classified as the control group (Fig. 1 and Table 2). The time course of the eosinophil counts was evaluated using the median

Table 1 Diagnostic criteria for late-onset circulatory collapse [11]

1. One week or longer since birth
2. No inotropic agent administered
3. Any of the following:
   - Mean blood pressure ≤80% of that in the previous stable state or systolic blood pressure <40 mmHg
   - Urine volume of ≤0.5 mL/kg/h over the past 8 h or ≤1.0 mL/kg/h over the past 24 h
4. No other apparent cause of hypotension (cardiac failure, dehydration, patent ductus arteriosus, or systemic infection)

counts of the infants in the control group at the postmenstrual age to avoid the effects of steroid treatment (Fig. 2). The eosinophil counts peaked at 30-31 weeks' postmenstrual age. Infants in the LCC group had significantly lower gestational ages and birth weights compared to those in the control group (Table 3).

We recorded the eosinophil counts both before and after steroid treatment in the 12 infants in the LCC group: the pre- and post-steroid median eosinophil counts were 0.877×10^9/L and 0.271×10^9/L, respectively. The post-steroid eosinophil counts were significantly lower than the pre-steroid eosinophil counts ($p=0.003$, Fig. 3).

The highest eosinophil counts during hospitalization in the LCC group were compared with those in the control group to avoid steroid treatment effects (Table 3). The peak eosinophil counts were significantly higher in the LCC group than in the control group, and the postmenstrual age was significantly earlier in LCC group, which reflected the onset of LCC.

Discussion

This is the first study to identify a relationship between eosinophilia and LCC in preterm infants. Our analyses revealed that the eosinophil counts were elevated under conditions in which steroid treatment for LCC was required. Earlier studies found that preterm infants are potentially in states of relative adrenal insufficiency due to reduced 3β-HSD activity, thus placing them at risk for LCC [13, 14]. Considering these findings together with the proposal that eosinophilia may reflect adrenal insufficiency [17], our results suggest that transient eosinophilia in preterm infants may be induced by relative adrenal insufficiency.

We observed that the eosinophil counts in the control group gradually increased after birth, reached a peak at 30-31 weeks' postmenstrual age, and subsequently decreased. The eosinophil counts reached a peak at 28 weeks in the LCC group. These results are similar to those reported in investigations in which almost all of the infants recovered from eosinophilia [1, 18, 19]. LCC is likely to occur at 28-29 weeks' gestation and peak at 2-4 weeks after birth [20], consistent with the eosinophil count trends identified in the present study. More premature infants need steroid treatment and have a higher peak eosinophil count. It may therefore be possible to predict the onset of LCC by prospectively following the time course of eosinophils, which will facilitate early intervention to prevent periventricular leukomalacia.

The results of our present analyses demonstrated

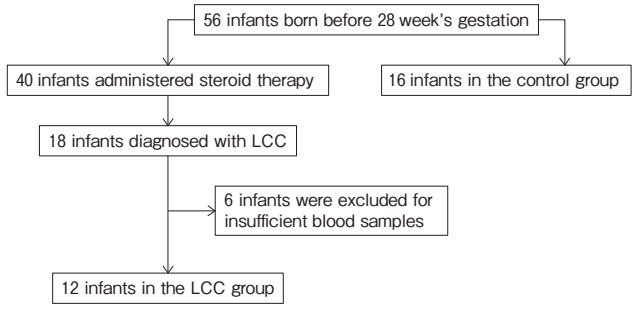

Fig. 1 Patient selection flow chart.

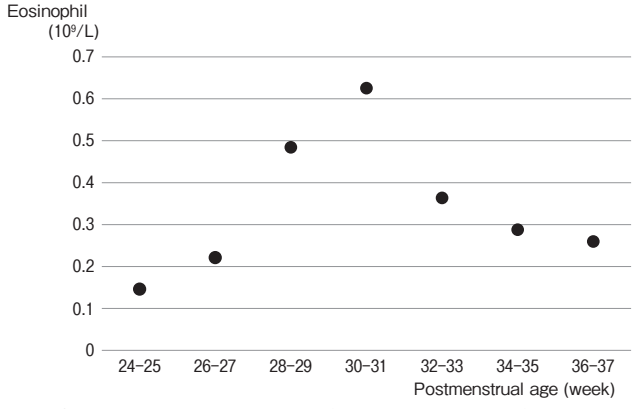

Fig. 2 Longitudinal transition of eosinophil counts of the control group.

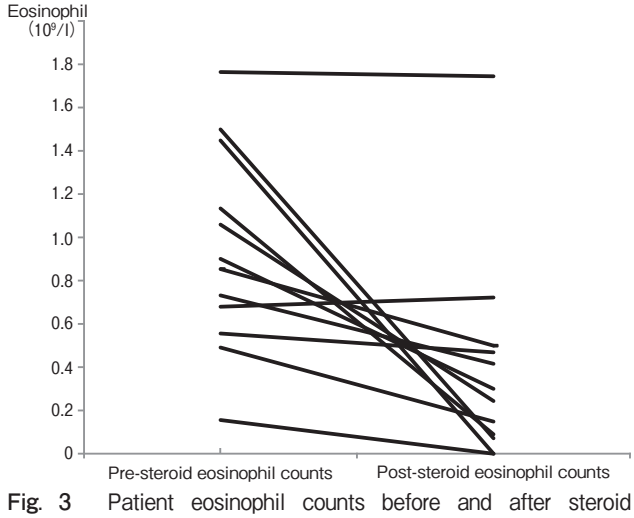

Fig. 3 Patient eosinophil counts before and after steroid infusion in the LCC group.

Table 2 Demographic and clinical characteristics of the infants

	LCC group (n = 12)	Control group (n = 16)	*P*-value
Gestational age* (week)	25.2 ± 1.5 (23–27)	26.4 ± 1.0 (24–27)	< 0.05
Birth weight* (g)	636 ± 159 (453–936)	905 ± 163 (580–1124)	< 0.05
Non-reassuring fetal status, n (%)	4 (33)	2 (13)	NS
Respiratory distress syndrome, n (%)	8 (67)	7 (44)	NS
Intraventricular hemorrhage (grade I and II), n (%)	4 (33)	2 (13)	NS
Chorioamnionitis, n (%)	1 (8)	6 (38)	NS

LCC, late-onset circulatory collapse; NS, not significant; SD, standard deviation.
* Values are the mean ± SD with the range in parentheses.

Table 3 Comparison of peak eosinophil counts during hospitalization between the LCC group and the control group

	LCC group (n = 12)	Control group (n = 16)	*P*-value
Postmenstrual age* (week)	28.0 ± 2.1 (25–31)	29.7 ± 1.7 (26–31)	0.03
Age in days ± SD, days	20 ± 7 (10–32)	23 ± 10 (11–44)	0.35
Peak eosinophil count (10^9/L)	1.392 (0.863–4.722)	1.033 (0.434–2.750)	0.02

LCC, late-onset circulatory collapse; NS, not significant; SD, standard deviation.
* Values are the mean ± SD with the range in parentheses.

that the infants' eosinophil counts after steroid treatment were lower than those before steroid treatment. Similar results have been reported [21]. Steroids are considered the most effective therapy for eosinophilia, and they suppress the production and lifespan of eosinophils by inhibiting cytokines such as granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin (IL)-3, and IL-5 [22]. Our results suggest that similar responses may occur in preterm infants. Steroid treatments may reduce the eosinophil counts in preterm babies by inhibiting cytokine production or activity.

This study has several limitations. First, despite the retrospective nature of the study, the sample size was small. The subjects were extremely premature infants with LCC, and it was thus inevitable that the sample size would be small based on the incidence ratio. Due to the small sample size, we did not perform a multivariate analysis, and we were thus unable to determine the role of other factors (*e.g.*, severe immaturity) that may have contributed to the development of eosinophilia in the LCC group. A future multicenter prospective study to further clarify the relationship between LCC and eosinophilia is being planned to address this limitation. A second limitation is that cytokines that affect eosinophilia (such as IL-3 and GM-CSF) were not evaluated. The assessment of these cytokines is essential in subsequent studies to elucidate the pathogenesis.

Our findings revealed a relationship between eosinophilia and LCC in preterm infants. Both eosinophilia and LCC may be caused by relative adrenal insufficiency. Therefore, eosinophilia is potentially a symptom of LCC.

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