

DOCTORAL THESIS

Cytokine profiles of tear fluid from patients with pediatric
lacrimal duct obstruction

(小児涙道閉塞症患者における涙液中サイトカインの分析)

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Cytokine Profiles of Tear Fluid From Patients With Pediatric Lacrimal Duct Obstruction

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PURPOSE. This study evaluated the cytokine levels in unilateral tear samples from both sides in patients with pediatric lacrimal duct obstruction.

METHODS. Fifteen cases of unilateral lacrimal duct obstruction (mean, 26.9 ± 28.7 months old) were enrolled in this study. Tear samples were collected separately from the obstructed side and the intact side in each case before surgery, which was performed under general anesthesia or sedation. The levels of IL-2, IL-4, IL-6, IL-10, TNF, IFN-γ, and IL-17A then were measured in each tear sample. A receiver operating characteristic (ROC) curve was constructed for the IL-6 levels in the tears. We also measured the postoperative tear fluid levels of IL-6 in those cases from which tear fluid samples could be collected after the surgery.

RESULTS. Only the IL-6 concentration was significantly higher on the lacrimal duct-obstructed sides, compared to the control sides ($P < 0.001$). An ROC curve analysis for the IL-6 levels in tears showed a high value for discriminating the lacrimal duct-obstructed side from the control side (area under the ROC curve [AUC], 0.99; 95% confidence interval [CI], 0.968-1). Significant decrease of the tear fluid IL-6 levels was observed in the seven cases from which tear fluid samples also could be collected after the surgery ($P = 0.016$).

CONCLUSIONS. The IL-6 level in tear fluid was significantly higher on the sides with lacrimal duct obstruction, compared to the control sides, and could be a biomarker for pediatric lacrimal duct obstruction.

Keywords: lacrimal duct obstruction, pediatric, tears, cytokine, interleukin

Congenital nasolacrimal duct obstruction (CNLDO) is the most common cause of pediatric lacrimal duct obstruction.^{1,2} The presence of a membrane covering the opening of the lacrimal duct has been reported to be the main cause of CNLDO.²⁻⁵ Chronic or acute dacryocystitis, blepharitis, and conjunctivitis often occur secondary to the obstruction of the lacrimal duct.^{1,2} Primary nasolacrimal duct obstruction is a common lacrimal disease in adults, and narrowing of the lacrimal lumen as a result of chronic inflammatory infiltrates and subsequent fibrosis is considered to be a major process.⁶ The levels of several inflammatory cytokines have been reported to be elevated in the tears of adults with primary acquired nasolacrimal duct obstructions.⁷ In a previous study, the levels of IL-2, IL-6, IL-10, VEGF, and FGF-2 were significantly higher in eyes with primary acquired nasolacrimal duct obstruction than in the controls, suggesting that IL-10 may have a potential role as a bioindicator for lacrimal passage obstruction.⁷ The mechanism underlying the increase in the cytokine levels in the tear fluid samples obtained from patients with lacrimal duct obstruction is not yet fully understood. The cytokines in the tears of patients with nasolacrimal duct obstruction are considered to be derived possibly from the mucosa-associated lymphoid tissue (MALT).⁷ The flow of tears through the lacrimal drainage system is a one-way system in

normal cases. However, in patients with lacrimal duct obstruction, the locally produced cytokines may flow back and accumulate in the tear film. Therefore, measurement of the tear fluid cytokine levels may be useful for evaluating lacrimal duct obstruction.

In pediatric populations, the cytokine concentrations in tears, regardless of the presence of lacrimal duct obstruction, have not yet been reported; therefore, whether any differences exist in the cytokine profiles of pediatric and adult populations remains unclear. While MALT is considered to be acquired during early childhood, the development and acquisition of MALT in humans remains to be fully clarified. Investigation of the cytokine profiles of tear fluid samples could serve as a key to understanding the development and acquisition of MALT during early childhood in humans.

To diagnose pediatric lacrimal duct obstruction and to evaluate its clinical severity, the dye clearance test and irrigation test are performed commonly.^{1,2} However, the results of the dye clearance test often are obscure to interpretation, while the irrigation test is invasive and necessitates the use of severe restraints in pediatric populations. Furthermore, since these methods also are not useful for quantitative evaluation, quantitative noninvasive or minimally invasive evaluation



methods have been sought for juvenile cases with lacrimal duct obstruction.

We evaluated the cytokine levels in unilateral tear samples from pediatric patients with lacrimal duct obstruction, comparing the normal and obstructed sides to investigate possible biomarker candidates for pediatric lacrimal duct obstruction.

METHODS

Patient Description

All patients were treated at the Kanagawa Children's Medical Center, Yokohama, Japan, between July 2015 and June 2016. We obtained approval for this study from the Institutional Review Board of the Kanagawa Children's Medical Center. All procedures were performed under the tenets of the Declaration of Helsinki, and informed consent was obtained from a guardian of each child. The study included 15 children (mean age, 26.9 ± 28.7 months) who underwent lacrimal surgery for unilateral lacrimal duct obstruction. Eight children underwent office-based lacrimal duct probing under sedation, receiving triclofos as premedication. Another seven children underwent lacrimal duct probing under general anesthesia at a surgical facility. Lacrimal duct obstruction was diagnosed based on clinical symptoms (epiphora and mucopurulent discharge) and a positive dye clearance test, and the failure of an irrigation test of the lacrimal drainage system. Slit-lamp examination with fluorescein staining was performed before surgery and a normal corneconjunctival fluorescein score was confirmed in all subjects. No patient suffered from any ocular or systemic disease other than lacrimal duct obstruction, and no patient had a medical history of any operation or commonly used medications. All patients underwent probing as a surgical intervention. A successful irrigation test was confirmed at the end of the surgery in all cases. All patients used steroid/antibiotic eye drops for up to 1 week after the surgery. The success of the treatment for lacrimal duct obstruction was confirmed based on the disappearance of the clinical symptoms (epiphora and mucopurulent discharge) and a negative dye clearance test.

Collection of Tear Samples

Tear samples were collected simultaneously from both sides in children with unilateral lacrimal duct obstruction under sedation or general anesthesia before an irrigation test or surgery. Tear fluid samples also were collected 1 month after the surgery. Since the postoperative tear fluid samples were collected in the awake state, they were obtained only from children who could cooperate without crying.

All samples were collected without the use of topical anesthesia and at least 6 hours after any previous eye drop instillation. All samples were collected between 10:00 AM and 3:00 PM in consideration of the diurnal rhythm.⁸ Tear fluid was collected using the Schirmer method.

All samples were rapidly frozen at -80°C until the cytokine analysis. Each sample was eluted from a filter paper in 50 μL of elution solution containing 0.5 M NaCl and 0.1% Tween 20 in 0.01 M phosphate buffer (pH 7.2), as described previously.⁹

Measurements of Cytokine Concentrations

The cytokine compositions of the tear samples were analyzed using the BD Cytometric Bead Array system (Becton Dickinson and Company, Franklin Lakes, NJ, USA) and a flow cytometer (BD FACS Cantoll), according to the manufacturer's instructions. Data were collected and analyzed using FCAP Array

TABLE. Comparison of Cytokine Expression Levels in Tears From Control Eyes and Eyes With Lacrimal Duct Obstruction

| Cytokine | Control, pg/mL | LDO, pg/mL | P Value* |
|---------------|------------------------|------------------------|----------|
| | Mean \pm SD (Median) | Mean \pm SD (Median) | |
| IL-2 | 0 (0) | 4.03 ± 15.6 (0) | - |
| IL-4 | 0 (0) | 3.25 ± 12.6 (0) | - |
| IL-6 | 28.0 ± 46.3 (0) | 666 ± 532 (467) | < 0.001 |
| IL-10 | 0 (0) | 2.66 ± 10.3 (0) | - |
| TNF | 0 (0) | 2.25 ± 8.71 (0) | - |
| IFN- γ | 3.04 ± 11.8 (0) | 10.1 ± 27.0 (0) | 0.96 |
| IL-17A | 36.7 ± 104 (0) | 93.7 ± 180 (0) | 0.37 |

LDO, lacrimal duct obstruction.

* Wilcoxon's rank sum test.

software (version 1.0.1; BD Biosciences, San Jose, CA, USA). Standard curves were generated using reference cytokine concentrations, which were supplied by the manufacturer. The following seven inflammatory cytokines were analyzed: IL-2, IL-4, IL-6, IL-10, TNF, IFN- γ , and IL-17A.

Statistical Analysis

All data were expressed as the mean \pm SD. The cytokine concentrations in the tear samples collected on the side of the lacrimal duct obstruction and those on the control side were compared using the Wilcoxon's rank sum test. Statistical significance was set at $P < 0.05$. To assess the diagnostic performance of IL-6 for pediatric lacrimal duct obstruction, analyses of the sensitivity and specificity were performed, and the data were finally summarized using receiver operating characteristic curves (ROC). An ROC analysis was performed, and the area under the curve (AUC) value was calculated. The optimal cutoff threshold was determined at the point on the ROC curve at which (sensitivity + specificity - 100%) was maximal. The IL-6 concentrations in the tear fluid samples collected preoperatively and postoperatively were compared using the Wilcoxon signed rank sum test. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

RESULTS

A total of 15 tear samples from the side with the lacrimal duct obstruction and 15 tear samples from the control side of the same patients were collected under the same conditions. A comparison of the cytokines levels in samples from the lacrimal duct obstruction and control sides is shown in the Table. Only the IL-6 concentration was significantly higher on the lacrimal duct obstruction side, compared to the control side (Table, Fig. 1).

Thereafter, we analyzed the ROC curve to determine the potential value of IL-6 in pediatric lacrimal duct obstruction (Fig. 2). The ROC analysis revealed that the IL-6 concentration in tear samples might be a potential biomarker for discriminating sides with lacrimal duct obstruction from control sides in pediatric populations. The AUC value was 0.99 (95% confidence interval [CI], 0.968-1; Fig. 2). The sensitivity and specificity were 92.9% and 100.0%, respectively, at a cutoff value of 129.88 pg/mL.

We could evaluate the preoperative to postoperative changes of the tear fluid IL-6 levels in seven cases, in all of whom the treatment was successful. This evaluation revealed a significant

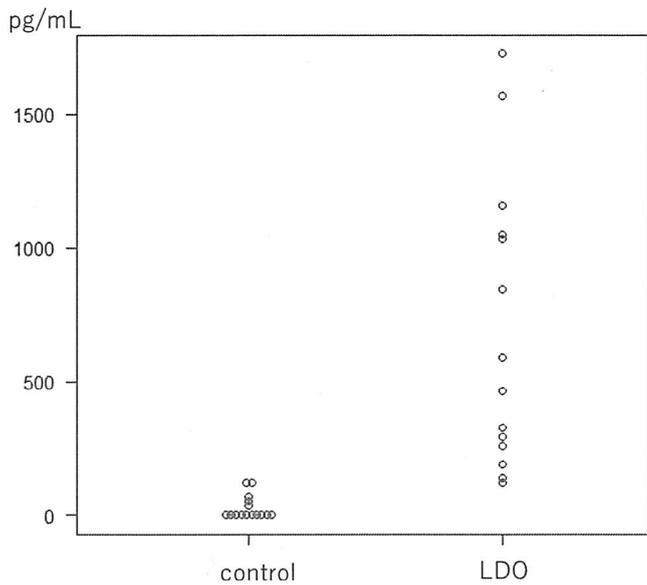


FIGURE 1. Comparison of the tear fluid IL-6 levels on the side of the lacrimal duct obstruction (LDO) and the opposite, control side. The IL-6 concentrations were significantly higher on the side of the lacrimal duct obstruction compared to those on the control side ($P < 0.001$).

decrease of the tear IL-6 levels postoperatively ($P = 0.016$; Fig. 3).

DISCUSSION

The tear fluid IL-6 level was significantly higher on the side of the lacrimal duct obstruction compared to that on the opposite, control side, and significantly decreased after surgical treatment. Thus, the tear fluid IL-6 concentration could be a useful biomarker for pediatric lacrimal duct obstruction. To our knowledge, the cytokine profiles in human

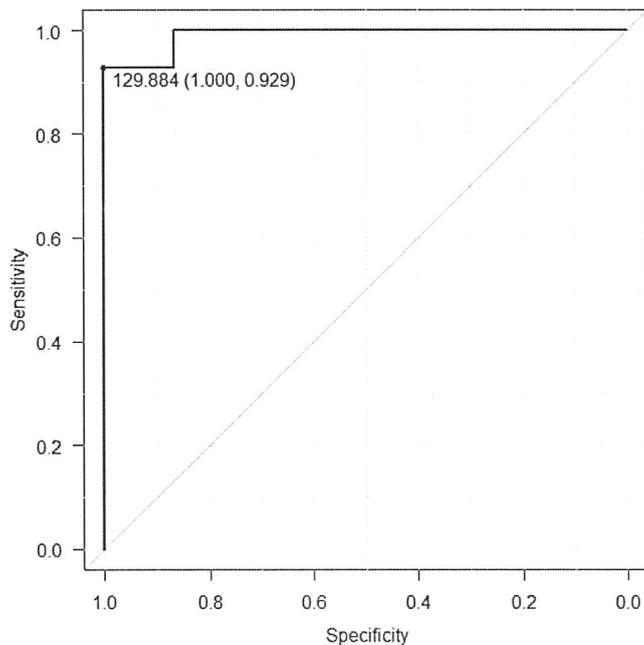


FIGURE 2. Receiver operating characteristic (ROC) curve for tear IL-6 levels in the diagnosis of pediatric lacrimal duct obstruction. Cut-off value = 129.88 pg/mL, AUC = 0.99 (95% CI, 0.968–1).

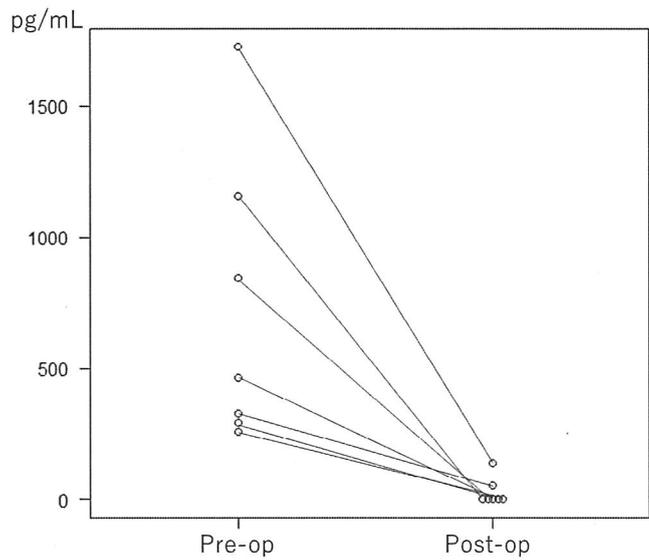


FIGURE 3. Comparison of the preoperative (preop) and postoperative (postop) IL-6 levels in tear fluid samples obtained from eyes with lacrimal duct obstruction. Significant decrease of the tear IL-6 levels was observed after the operation ($P = 0.016$, Wilcoxon's signed rank sum test).

tears from pediatric populations have not been reported previously; thus, this may be the first report on this topic. According to a previous report, the IL-2, IL-6, and IL-10 levels in tears were significantly higher in eyes with primary acquired nasolacrimal duct obstruction than in control samples, suggesting that IL-10 might have a potential role as a bioindicator in adult populations.⁷ In the present study, only the tear IL-6 level was significantly higher on the side with lacrimal duct obstruction, compared to the control side. The reason for this discrepancy is not clear. In pediatric populations, CNLDO is the most common cause of lacrimal duct obstruction,^{1,2} which is thought to occur as a result of congenital anatomic problems.^{1–4} Therefore, an elevation in the tear IL-6 level might indicate the presence of a secondary inflammation, such as dacryocystitis. On the other hand, primary nasolacrimal duct obstruction in the adult population is considered to occur as a result of chronic inflammatory infiltrates and subsequent fibrosis.⁶ These differences might explain the different cytokine profiles of lacrimal passage obstruction between adult and pediatric cases. Because IL-6 has been reported to shift acute inflammation into a more chronic profibrotic state,¹⁰ high levels of tear fluid IL-6 might drive more severe inflammatory fibrosis of pediatric lacrimal duct obstruction.

Tear cytokine levels have been reported to be significantly elevated in several conditions. Interleukin-6 has been reported to be the key cytokine in dry eye disease.^{11–13} In addition, there are many reports about tear cytokine profiles, such as in corneal diseases,^{14,15} keratoconjunctivitis,^{16,17} meibomian gland disease (MGD),^{11,18} contact lens wearers,^{19,20} cases with medical histories of ophthalmic surgery,^{18,21,22} and systemic diseases, like diabetes.²³ Most of these studies have focused on adult populations; thus, these results are not necessarily applicable to our study of the cytokine profiles in tears from eyes with lacrimal duct obstruction in children. Because none of the children suffered from any ophthalmic or systemic disease other than lacrimal duct obstruction in the present report, a simple comparison of the cytokine profiles between tears from eyes with and those without lacrimal duct obstruction was possible.

Interleukin-6 is considered to be a major proinflammatory cytokine and is important for protection against pathogens during an infection.^{24,25} Interleukin-6 also is considered to have an important role in CD4 T cell differentiation.^{24,25} Although the origin of the elevated tear IL-6 levels was not identified in the present study, they likely derive from MALT. Mucosa-associated lymphoid tissue is considered to have a specific protection role on mucosal surfaces.²⁶ The ocular mucosal immune system (OMIS) is considered to be comprised of conjunctiva-associated lymphoid tissue (CALT) and tear duct-associated lymphoid tissue (TALT).²⁶⁻³⁰ According to these previous reports, TALT is considered to be a preferential site for the uptake of ocularly encountered pathogens and for the subsequent induction of antigen-specific B cell responses. In the present report, the high concentration of IL-6 in tears from eyes with lacrimal duct obstruction in pediatric patients might reflect these specific immunoresponses of OMIS in children. The development and acquisition of OMIS in humans remains to be clarified. Tear duct-associated lymphoid tissue has been identified in only 30% to 40% of humans examined in adult populations.^{27,30} Previous reports suggest that MALT is absent in neonates and is acquired during early childhood.^{29,30} The initial stimulation of B cells is believed to occur mainly in organized MALT.³¹ In the present report, IL-2, -4, and -10 or TNF was not detectable in any of the control samples, although all of these are detected in tear fluid samples of adult populations.^{7,8,11,16,22} The reason for this discrepancy is not clear, but the absence of these cytokines might be explained by some immunologic prematurity of OMIS in pediatric populations. To clarify the details, further investigations of other cytokine profiles are necessary.

To diagnose pediatric lacrimal duct obstruction and to evaluate its clinical severity, a dye clearance test and an irrigation test are performed commonly for the lacrimal ducts.^{1,2,32} However, a quantitative evaluation method for lacrimal duct obstruction in juvenile cases has not yet been established to our knowledge. In the present study, we demonstrated that the tear fluid levels of IL-6 were significantly elevated on the side of the lacrimal duct obstruction and that these levels decreased after successful surgical treatment. The tear IL-6 concentration was shown to be a potential biomarker for pediatric lacrimal duct obstructions, and this parameter might be useful not only for diagnosis, but also for the evaluation of severity and as a predictor of treatment results.

There are some limitations in the present study. Because tear collection is difficult to perform during infancy while the subject is awake, the number of cases was limited. With this in mind, the further accumulation of samples is necessary. Also, we only investigated seven kinds of cytokines in the present study, and additional studies of other types of cytokines are required to survey this subject in detail.

In conclusion, an elevated IL-6 level in tears from eyes with lacrimal duct obstruction might be useful as a biomarker for pediatric lacrimal duct obstruction and might reflect the immunologic characteristics of this disorder.

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I 主論文

Cytokine profiles of tear fluid from patients with pediatric lacrimal duct obstruction

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II 副論文

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