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Changes in Tears Monocyte Chemoattractant Protein-1 Level After External Dacryocystorhinostomy in Primary Acquired Nasolacrimal Duct Obstruction

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Background: The authors aimed to define tears monocyte chemoattractant protein-1 (MCP-1) changes after external dacryocystorhinostomy surgery.

Materials and Methods: Tears samples were collected with a Schirmer strip and stored in Eppendorf tubes at −80°C. At the end of the study, the papers were cut into small pieces and incubated with phosphate-buffered saline solution. Monocyte chemoattractant protein-1 levels were determined by using an enzyme-linked immunosorbent assays kit.

Results: The MCP-1 levels were 498.66 ± 101.35, 576.40 ± 149.78, 422.53 ± 85.94, and 436.96 ± 81.38 ng/L before surgery, in the first week, the first, and third months after surgery, respectively. Its level significantly increased in the first week compared with the preoperative level ($P < 0.001$). There was a prominent decrease in the postoperative first month ($P < 0.001$). In the third postoperative month, the mean MCP-1 level was not significantly increased compared with the postoperative first month ($P = 0.196$).

Conclusion: The tears MCP-1 level was significantly decreased after external dacryocystorhinostomy surgery.

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Primary acquired nasolacrimal duct obstruction (PANDO) arises from idiopathic nasolacrimal duct (NLD) inflammation that results in obstructive fibrosis of the lumen not accompanied by secondary causes such as neoplastic, traumatic, or mechanical origins. External, endoscopic, and endonasal laser dacryocystorhinostomy (DCR) with or without silicon stents have been commonly used surgical techniques to treat PANDO with a variant success rate.1,2 External dacryocystorhinostomy (ext-DCR) provides direct visualization of the surgical area without requiring additional devices such as flexible or rigid nasal endoscopies. A meta-analysis showed that silicon tube intubation did not enhance postoperative complications such as granulation, infection, and adhesion.3 Moreover, it prevents the ostium's occlusion and increases the surgery's success rate.3,4

In etiology, various factors such as infections, hormones, tears integrity, drugs, and anatomical variation of adjacent structures have been proposed.5–8 Studies showed some changes in tears inflammatory [interleukin (IL)-1-2-6], anti-inflammatory (IL-10) cytokines, and growth factors to clarify the biological pathways of the etiology.9

Monocyte chemoattractant protein-1 (MCP-1) is a particular type of cytokine and an effective chemoattractant that has a primary role in monocytes and macrophages migrations to the inflammation sides.10 As we know, there has been no study revealing the tears MCP-1 changes after any type of DCR in PANDO. This prospective, longitudinal study determined changes in tears MCP-1 level after uncomplicated ext-DCR with bicanalicular silicone tube intubation (BCSI) in PANDO.

MATERIALS AND METHODS

In this prospective, longitudinal study, we included the patients who applied to the ophthalmology clinic with epiphora, were diagnosed as PANDO and underwent ext-DCR with BCSI in 1 or both eyes between December 2019 and February 2021. All the patients had epiphora symptoms for at least 6 months when they enrolled in the study. Primary acquired nasolacrimal duct obstruction was diagnosed performing lacrimal irrigation with a 27-G cannula through the dilated upper and lower punctum without flowing the isotonic saline to the throat or nose.

Patients were carefully examined with a biomicroscopy and nasal endoscopy to rule out pathologies of nasal, lacrimal, and adjacent tissues. Patients with congenital or secondary acquired NLD obstruction caused by nasal and paranasal pathologies (septal deviation, nasal cavity masses, sinüsitis, etc.), primary or metastatic lacrimal system tumors, naso-orbital fractures, mechanical reasons (eg, dacryoliths), active anterior segment and lacrimal system infective-inflammatory pathologies (dacryocystitis, dacryoadenitis, conjunctivitis, keratitis, etc.), eyelid-eyelash pathologies (eg, entropion, ectropion, distichiasis, trichiasis), history of ophthalmic surgery in the last 3 months and surgery at any level of the lacrimal drainage system, systemic autoimmune diseases (sarcoidosis, Sjogren disease, Wegener granulomatosis, etc.), and had been using topical-systemic steroids, immunosuppressive-immunomodulatory, or antiglaucoma drugs were excluded.

All the operations were undertaken by a single surgeon (M.K.) under general anesthesia. On the operated side, lignocaine and adrenaline-soaked gauze were applied through the nostril to the lateral nasal mucosa to minimize bleeding. After a 12 mm vertical skin incision below the medial canthal ligament, the orbicular muscle was split with a monopolar cautery with the help of vein retractors until the periosteum was reached. The periosteum was incised and dissected to expose the lacrimal sac. The nasal mucosa was exposed after opening for about 10 to 15 mm bone hole. The nasal gauze was taken out, and the "H shaped" incision was applied to the nasal mucosa and lacrimal sac to create flaps. Posterior flap suturing, BCSI, and anterior flap suturing were performed. All the tissues were closed by suturing in layers. The silicon tube was freely released to the nasal cavity after forming a square knot. For the incision side, tobramycin % 0.3 ointments (Tobrased opt. pomade, Bilim Pharmaceuticals Inc, Istanbul, Turkey) 3 times a day for 1 week was prescribed. Patients also received a combination of loteprednol etabonate 0.5% and tobramycin 0.3% opt. susp. (Zylet, Bausch & Lomb Inc, Rochester, NY), and mometasone furoate % 0.05 nasal spray (Nazoster, Santa Pharma Inc, Istanbul, Turkey) 4 times a day for 2 weeks. The skin sutures were removed during the first postoperative week. The silicon tubes stayed at least 4 months.

Tears samples were collected 1 day before surgery, in the first week, the first, and the third month after surgery. Tears samples were collected with a Schirmer strip placed lateral conjunctival cul-de-sac for about 5 minutes until at least 15 mm of the strip was filled with tears. The amount of tears was calculated in microliters with a regression graph corresponding to the Schirmer strips. The samples were stored in Eppendorf tubes at −80°C within 10 minutes after sampling.

At the end of the study, the samples were taken out of the −80°C cabinet and brought to room temperature. The papers were cut into small pieces and incubated in 2 mL tubes with phosphate-buffered saline solution at room temperature in a shaker at 100 revolutions per minute (rpm) for about 3 hours. Then they were centrifuged at 1000 rpm for 5 minutes. Monocyte chemoattractant protein-1 concentrations were measured in tears using human-specific enzyme-linked immunosorbent assays (BT-Laboratory, Shanghai, China) according to the manufacturer's instructions. Monocyte chemoattractant protein-1 assay sensitivity was 2.43 ng/L with interassay and intra-assay coefficients of variation <10% and 8%, respectively. The statistical program recorded the data and represented the mean ± SD for continuous variables and frequencies (percentages) for categorical variables. Friedman analysis of variance and Wilcoxon tests were used for repeated measures analysis and pairwise comparisons. $P < 0.05$ was defined as statistically significant. Power analysis was performed using GPower 3.1 software.

Muğla Sitki Koçman University Clinical Research Ethics Committee approved this study with a 06/VI decision number. All patients provided informed consent. The Declaration of Helsinki's principle was consistently followed throughout the study.

RESULTS

Thirty-two eyes of 30 patients who met the inclusion criteria were included. However, 3 eyes of 3 patients who did not attend at least 1 of 3 postoperative visits and 2 eyes of 2 patients with recurrent obstruction were excluded. Post hoc power calculations were applied, and the sample size was seen to provide 0.989 power and 0.808 effects size for MCP-1 at α error probability level of 0.05. The silicone tubes were in place in all eyes in the third month of the surgery. None of the remaining patients developed postoperative complications such as wound infection, dehiscence, silicon tube prolapse,

rhinostomy fibrosis, and intranasal synechiae. Of the patients, 14 (56%) were female, and 11 (44%) were male. The mean age was 52.7 ± 10.3 years (range, 30–63 y), as shown in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/SCS/E336).

The MCP-1 levels were 498.66 ± 101.35, 576.40 ± 149.78, 422.53 ± 85.94, and 436.96 ± 81.38 ng/L before surgery, in the first week, the first, and third months after surgery, respectively. There was a significant difference among these values ($P < 0.001$), as shown in Supplemental Table 2 (Supplemental Digital Content 2, http://links.lww.com/SCS/E337).

The mean MCP-1 level significantly increased in the first week compared with the preoperative level ($P < 0.001$). There was a prominent decrease in the postoperative first month compared with the preoperative level ($P < 0.001$). In the third postoperative month, the mean MCP-1 level was not significantly increased compared with the postoperative first month ($P = 0.196$) (Fig. 1).

DISCUSSION

This prospective, longitudinal study showed that the tears MCP-1 level significantly increased in the postoperative first week and had a prominent decrease in the postoperative first month compared with the preoperative level after uncomplicated ext-DCR with BCSI surgery. Compared with the postoperative first month, it was not significantly changed in the postoperative third month, and its low level was continued.

The etiopathogenesis of PANDO has not been well understood yet. On the other hand, changes in tears proteins and electrolytes dysregulation of some biological pathways in NLD epithelium, such as increased inflammation, cellular proliferation, and decreased apoptosis, have been thought to be associated with NLD lumen obstruction.7,9,11,12

In some studies, the alterations of the tears inflammatory and anti-inflammatory cytokines and growth factors have been demonstrated to clarify the etiopathogenesis of PANDO. Ali et al7 reported upregulation of 10 proinflammatory and 3 anti-inflammatory cytokines in tears of eyes with PANDO compared with the healthy fellow and control eyes. In a comparative study, Lee and Kim9 demonstrated that IL-1, IL-6, IL-10, transforming growth factor-β2, fibroblast growth factor-2, and vascular endothelial growth factor significantly increased in eyes with PANDO compared with the normal eyes, and a significant decrease was shown in these cytokines after endoscopic DCR. Andalib et al13 showed in a case–control study that IL-1β level was predominantly increased in eyes with PANDO in comparison with the healthy fellow and control eyes.

Acute inflammation begins fast and proceeds a few days or weeks, whereas chronic inflammation lasts for months or years. Monocyte chemoattractant protein-1 is a cytokine that regulates monocyte migration and infiltration in the inflamed area in acute and chronic inflammations.14 Increased ex-

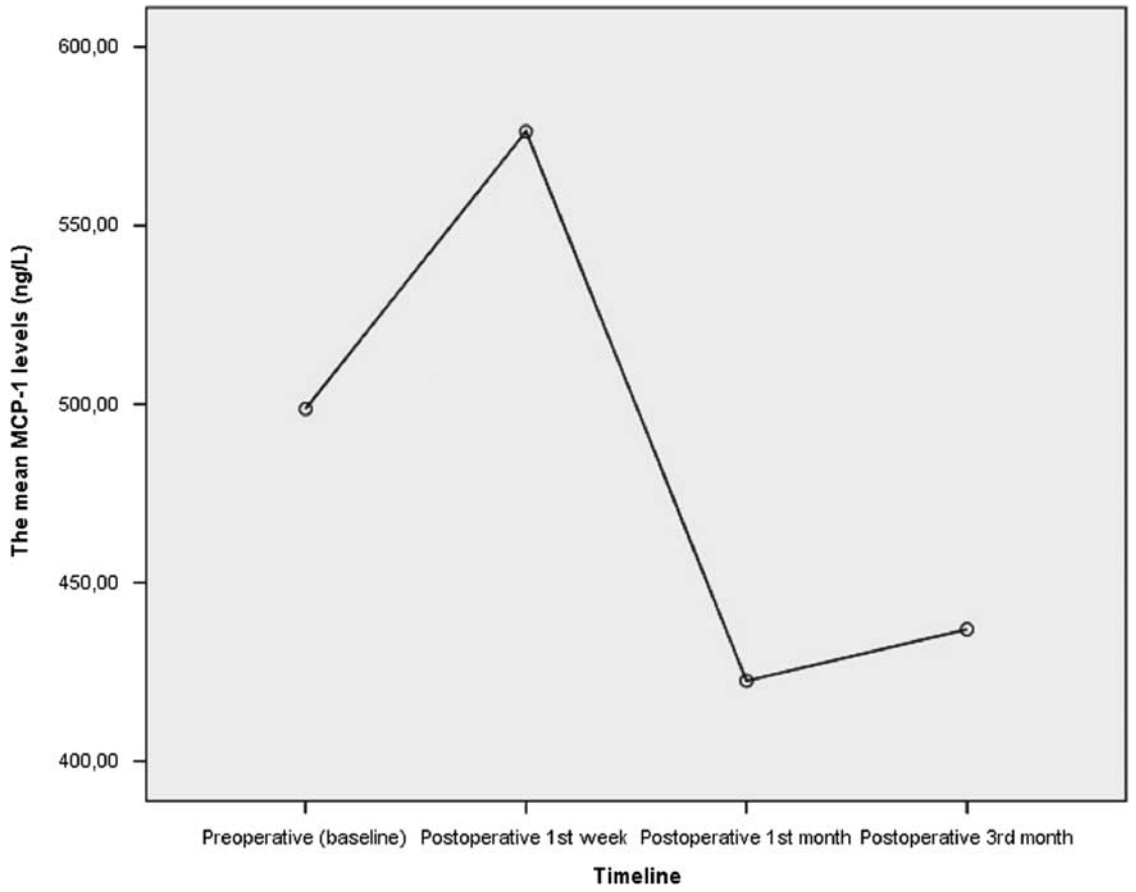

FIGURE 1. The tears MCP-1 level changes over time. It was significantly increased in the postoperative first week ($P < 0.001$), and there was a dramatic decrease in the postoperative first month ($P < 0.001$). The mean MCP-1 level change was not significant in the postoperative third month compared with the first month ($P = 0.196$). MCP-1 indicates monocyte chemoattractant protein-1.

pression of MCP-1 was reported in vitreous samples of the eyes with retinal detachment, diabetic retinopathy, and in aqueous humor samples of eyes after phacoemulsification surgery.15–18 As pterygium and dry eye syndrome were chronic inflammatory disorders, it was thought that high expression of MCP-1 might have a role in the etiopathogenesis of these diseases.19 In addition, in patients with Stevens-Johnson syndrome, dramatically increased tears MCP-1 level was demonstrated.20,21

To the best of our knowledge, there has been no study indicating the tears MCP-1 level changes after ext-DCR with BSTI in PANDO. Our study found a significant increase in the tears MCP-1 level in the first week compared with the baseline. We thought this increase could be originated from the inflammation and proliferation stage of the wound healing process. In the first month, its level was dramatically decreased compared with the first week and baseline. Besides, the lower level of MCP-1 continued and was not significantly changed in the third month compared with the first month. Our patients were prescribed topical loteprednol etabonate 0.5% and intranasal mometasone furoate % 0.05 spray 4 times a day for 2 weeks. Topical and intranasal steroids could accelerate the decrease of tears MCP-1 level. However, these steroids have a short half-life and are eliminated rapidly.22,23 Therefore, administration of these steroids for 2 weeks after surgery could not have reduced the tears MCP-1 level in the first and third months. So we thought that the decrease of the tears MCP-1 level in the first and third months was not related to 2 weeks administration of these steroids. Instead, this dramatic decrease in the first month and stable duration might be related to resolving the tears drainage failure. Previous studies have supported our hypothesis by indicating that tears clearance insufficiency may induce inflammatory cytokines due to ocular surface irritation.24,25

This study was limited in some ways. The duration of the study was relatively short, and the silicone stents were not removed at the end of the study. Extubation of the silicon tubes and long study duration might have affected the results. Besides, we only showed the changes of the tears MCP-1 level after ext-DCR with BCSI in PANDO. We did not compare it with the tears of fellow eyes and age, sex-matched healthy controls.

In conclusion, the tears MCP-1 level was significantly decreased after ext-DCR with BCSI in PANDO. These results might be interpreted as that uncomplicated ext-DCR with BSCI reduces inflammation by enhancing tears flow clearance and relieving ocular irritations. Prospective studies with a prolonged follow-up are needed to demonstrate this surgery's long-term effects on tears cytokine levels.

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